

**TOPICAL ANTI-CANCER COMPOSITIONS  
AND METHODS OF USE THEREOF**

**CROSS-REFERENCES TO RELATED APPLICATIONS**

5           This application is a continuation-in-part of U.S.  
Patent Applications Serial Nos. 09/698,454, filed  
October 27, 2000, and 10/108,248 filed March 27, 2002,  
the entire disclosure of which are incorporated by  
10       reference herein.

**FIELD OF THE INVENTION**

          This invention relates to compositions containing  
non-denatured soy products, or soy trypsin inhibitors,  
15       and optionally additional anti-cancer or cosmetically  
active agents. These compositions can be applied  
topically to reduce the risk of UV-induced cutaneous  
tumors.

20                               **BACKGROUND OF THE INVENTION**

          Skin, the largest organ of the human body, is  
continuously exposed to environmental insults such as  
smoke, pollution, and ultraviolet (UV) irradiation. The  
thinning of the ozone layer, which is expected to  
25       progress for at least several decades, reduces a major  
barrier to the passage of ultraviolet-B radiation (UVB)  
through the atmosphere. UVB, that is, light whose  
wavelength is in the range between about 280 and about  
320nm, is the main cause of sunburn, tanning, aging of  
30       the skin, and skin cancer.

          The non-melanoma skin cancers (NMSC), including  
basal-cell and squamous-cell carcinoma, are the most  
common types of cancer among Caucasian populations. The  
incidence of NMSC has increased worldwide over the last  
35       few decades. Increased recreational and occupational

sunlight exposure is commonly regarded as one of the reasons for the higher incidence of cutaneous cancers. The increase in UVB exposure associated with the thinning of the ozone layer is another significant factor. Mortality from NMSC is low, but the estimated recurrence rate of about 50% after five years and the local invasiveness of this type of cancer result in high medical costs. Therefore, NMSC constitutes a substantial public health concern. (Reviewed in Holick and Kligman, editors: Biologic effects of light. Walter de Gruyter, Berlin and New York, 1992).

Photo-carcinogenesis results from a complex interplay of simultaneous and sequential biochemical events. These events, initiated by irradiation of an organism with UV light of an appropriate wavelength, include the formation of DNA photo-products, inaccuracies in DNA repair, mutation of proto-oncogenes and tumor suppressor genes, and UV-induced production of radical species which produce subsequent effects on existing mutations and independently induce further mutations. In addition, other epigenetic events such as immunological responses, antioxidant defenses, and dietary factors may influence the course of carcinogenesis. (Black, H.S., deGruijl, F.R., Forbes P.D., Cleaver, J.E., Ananthaswamy, H.N., deFabo, E.C., Ullrich, S.E., Tyrrell, R.M., Photo-carcinogenesis: an overview. J. Photochem. Photobiol. B 40:1, 29-47, Aug., 1997).

The skin possesses an elaborate antioxidant defense system to deal with UV-induced oxidative stress. Excessive exposure to UV radiation, however, can overwhelm the cutaneous antioxidant capacity, leading to oxidative damage and ultimately to skin cancer and premature skin aging. Therefore, one strategy for

70 photo-protection is to support the endogenous  
antioxidant system by induction or transdermal delivery  
of antioxidant enzymes or nonenzymatic antioxidants.  
Antioxidants such as glutathione, alpha-tocopherol,  
ascorbate and beta-carotene have been found to be very  
75 effective in photoprotection. Components of the  
antioxidant pathway have also been identified and  
applied to the skin of patients. Although skin  
treatments with single components of the antioxidant  
system such as vitamin E were successful against a wide  
80 variety of types of photodamage, they were not shown to  
affect the progression of UV-induced tumors. The most  
promising results were obtained in studies combining  
several compounds, which often resulted in synergy  
between the protective effects. (Steenvoorden D.D., van  
85 Henegouwen G.M., The use of endogenous antioxidants to  
improve photoprotection, J. Photochem. Photobiol., B  
41:1-2, 1-10, Nov., 1997).

Epidemiological studies suggest that components of  
vegetables, particularly legumes, are beneficial in  
90 lowering the incidence rates of many types of cancer.  
For example, the rates of breast, colon and prostate  
cancer are significantly lower among the inhabitants of  
most countries of the Pacific Basin, but offspring of  
Pacific Basin natives who have migrated to the United  
95 States develop the common Western cancers at  
approximately the same rate as native Westerners. Such  
epidemiological studies suggest that dietary and other  
environmental factors, rather than genetic differences,  
contribute more significantly to the risk of  
100 susceptibility to these cancers. The high consumption of  
soybean products in Pacific Basin countries, such as  
Japan, implicates diet as one factor contributing to the  
relatively extremely low rates of cancer mortality in

these countries. (E.g., Wu et al., Soy intake and risk  
of breast cancer in Asians and Asian Americans. Am. J.  
Clin. Nutr. 68: 6 Suppl., 1437S-1443S, Dec., 1998).

Soybeans are a rich source of isoflavones, which  
possess weak estrogenic activity. Genistein, the main  
soybean isoflavone, is a specific inhibitor of protein  
tyrosine kinases and of other enzymes involved in signal  
transduction. Genistein has been shown to suppress the  
growth of numerous cancer cells *in vitro*, and to protect  
animals in experimental carcinogenesis models from  
developing both hormone- and non-hormone related  
cancers. (Reviewed in A. R. Kennedy, Chemopreventive  
agents: Protease inhibitors, Pharmacology Theories 78  
(3), 167-209), 1998 and in Messina et al., Soy intake  
and cancer risks: A review of the *in vitro* and *in vivo*  
data, Nutrition and Cancer 21 (2), 113-131, 1994).

Soybeans also contain a number of protease  
inhibitors such as BBI and STI. It is important to note  
that soy foods do not contain high concentrations of  
active STI and BBI, because these protease inhibitors  
block the action of trypsin and other enzymes needed for  
protein digestion. Although STI is denatured by cooking,  
heat alone does not inactivate BBI, and consumption of  
soy products containing high levels of these protease  
inhibitors leads to serious digestive problems, chronic  
deficiency in amino acid uptake, and cancer. Indeed,  
the Chinese did not serve soybeans as food until  
fermentation techniques were developed to destroy the  
anti-digestive properties of the soy foods (2nd century  
B.C.E.). During the production of soy foods today,  
pureed soybeans are soaked in an alkaline solution and  
then pressure-heated to 115<sup>0</sup>C in order to denature the  
protease inhibitors as much as possible.

Limtrakul et al. attempted to identify a safe level of soy proteins for nutritional consumption, which would be beneficial in the prevention of cancer. Skin tumors  
140 were chemically induced in mice, which were fed soy protein isolate (SPI) exclusively, and in mice which were fed SPI supplemented with soymilk proteins (SMP). It was reported that "the percentage of tumor-bearing mice and the volume of tumor tended to be lower in the  
145 mice on the SMP diet". *Life Sciences* 1993, 53, 1591-1596. When defatted soybeans are treated first with alkaline, then with acid solution, SPI is the precipitate and SMP is the supernatant. The Limtrakul study shows the potential of soy proteins to affect skin  
150 cancer progression, when the proteins are orally consumed. However, it was also emphasized that higher levels of dietary intake of SMP would result in major health problems.

It is clear that a need exists for safe,  
155 efficacious and economical agents that prevent or reduce incidence of cancer, particularly for NMSC, which may be simply and conveniently administered. Further, economical and prophylactic compositions and methods for the reduction, prevention or inhibition of the  
160 progression of UV-induced cutaneous tumors are highly desirable. Since topical application is very simple and convenient, incorporating compositions that reduce skin cancer incidence into a skin-care product would be extremely advantageous. While sunscreens are known to  
165 reduce the damage resulting from UV exposure during the period of their application, there is a need for a skin care product that could also slow the progression of already-initiated photocarcinogenic processes. It is an object of the invention to provide such a product.

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## SUMMARY OF THE INVENTION

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The present invention provides a method of reducing the risk of developing UV-induced tumors of the skin of a mammal by topically applying a skin-care composition, preferably in a preventive, pretreatment fashion, and on a daily basis, to skin areas that might be exposed to or irradiated with UV light. A method of reducing or preventing the DNA and cellular damage induced by UV irradiation by topically applying the skin-care composition is also provided.

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The skin care composition for use in the methods of the invention is formulated for the topical delivery of a non-denatured soy product (e.g., to a mammal such as a human) and comprises a soy product (e.g., a non-denatured soymilk or soybean powder or soybean trypsin inhibitor) and a vehicle. The composition may optionally comprise other anti-cancer or cosmetically active agents. Certain skin care compositions appropriate for use in the present invention have been described in U.S. Patent Application Nos. 09/110,409, 09/621,565 and 09/698,454, filed July 6, 1998, July 21, 2000 and October 27, 2000, respectively, and in International Application No. WO99/04752. Each of the foregoing patent documents is incorporated herein by reference.

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Other features and advantages of the present invention will be apparent to those of skill in the art in light of the following description and claims.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

200 It is believed that one skilled in the art can, based upon the description herein, utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure.

205 All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The present invention is directed to soy-containing compositions and methods of use thereof in the

210 prevention and reduction of the risk of skin cancer. The novel compositions of this invention contain legume products, and preferably soy products, that may be in the form of a fluid (e.g., soymilk) or a solid (e.g., a soybean powder or soymilk powder). What is meant by

215 "soy product" is a substance derived from the soybean, containing the ingredients naturally found in soybeans, at the relative concentrations as found in the beans, excluding water content. In one embodiment, the soy product is a non-denatured soy product.

220 "Denaturation" is defined in the Bantam Medical Dictionary (1990 edition) as "the change in the physical and the physiological properties of a protein, that are brought about by heat, X-rays or chemicals. These changes include loss of activity (in the case of

225 enzymes) and loss (or alteration) of antigenicity (in the case of antigens)".

What is meant by "non-denatured soy product" is a soy product in which the processing for the derivation of such soy product (e.g., the temperature, extraction

230 media) did not eliminate its protease inhibitory activity. In one embodiment, the non-denatured state of the soy product of this invention is measured by the

presence of an intact soybean trypsin inhibitor (STI) protein.

235           In another embodiment, the soy product is soymilk. One way to make soymilk is to soak the soybeans in deionized or purified water for several hours, and grind them after they were fully hydrated, with the addition of small quantities of water. (The grinding process  
240           allows the soybean milk to be extracted). After collection, the soybean milk may be filtered to remove any residual parts of the bean husk. The soymilk used in this invention can be fresh soymilk as described above, or may be made from soybean powder and water.  
245           The soybean powder is milled from soybeans and may also be lyophilized, spray dried, or freeze-dried and the resulting soymilk may or may not be filtered. Soymilk prepared by these methods may have from about 1 to about 90% by weight dry soybean powder. Another example is  
250           the use of soymilk powder, made from lyophilized, spray dried or freeze-dried soymilk, with the addition of water and finished with or without filtration or homogenization.

          Other methods of soybean extraction could also be  
255           used to create the active ingredients used in this invention. In one example, the active ingredients could be extracted from ground soybeans using ethanol/water mixtures, followed by the removal of the ethanol from the extract, in such ways that the protease inhibitory  
260           activity of the soybean will be retained.

          The compositions of the present invention may contain from about 1% to about 99%, by weight, of the soy product. For example, when a liquid soy product (e.g., soymilk) is used, the composition may contain from about  
265           50% to about 99%, by weight, (e.g., from about 70% to about 99%) of the liquid soy product. For example, when



a solid soy product (e.g., soybean powder or soymilk powder) is used, the composition may contain from about 1% to about 50%, by weight (e.g., from about 2% to about 30%, by weight) of the solid soy product. Compositions comprising solid soy products may also comprise water (e.g., distilled water or water contained within soymilk) to form a liquid base for the composition (e.g., to form a cream, lotion, injectable solution or gel). Such compositions may comprise from about 50% to about 98%, by weight (e.g., from about 70% to about 98%, by weight) of water. While not limited to these methods of administration, the compositions of this invention may be delivered topically, orally, or parenterally, although topical administration is preferred.

The soy products useful in this invention may be produced from all soybean species, regardless of their geographic origin, sun exposure, harvest time and the like. However, specific strains, geographic origins or growth conditions might be preferred. These include soybean strains or other legume strains particularly rich in their trypsin inhibitor (e.g. STI, LTI, BBI) content or strains in which, under the proper growth conditions trypsin inhibitor enrichment occurs in the bean. It should be noted that the legume products useful in the compositions of this invention have a distinctive odor, which may be tolerable in some cultures, but is undesired in others. If necessary, the odor of the compositions of this invention can be reduced by using soybean products derived from specific strains of soybeans known to be less odiferous, including, but not limited to, lipoxxygenase-2-deficient beans and those having a modified sugar profile, or the like. A process to reduce oxygen levels in the formulation may also reduce

300 the odor. Various masking agents or fragrances may also be used to mask the odor.

In yet another embodiment of the invention, the soy-containing compositions may optionally comprise additional synthetic or natural anti-cancer agents. 305 Examples of such agents include, without limitation, caffeine, Milk Thistle extract, green tea extract, epigallocatechin gallate, silymarins, glucocorticoids and 5-fluorouracil.

A preferred embodiment of the invention comprises 310 the administration of soymilk containing compositions before or after the initiation of UV-induced skin cancer. Especially preferred are embodiments in which the soymilk is not denatured, leaving STI and BBI intact. Soymilk also contains genistein and other 315 isoflavones, and anti-oxidants such as the gamma form of vitamin E, which is essential to the health of the skin. While not wishing to be held to any particular theory, it is hypothesized that these different active components also participate in the prevention of tumor 320 progression. Soymilk also contains lecithins and other emulsifying molecules that facilitate the transdermal delivery of the active components.

As explained above, the present invention extends to a topical cosmetic or pharmaceutical composition 325 comprising a non-denatured soy product (e.g., a non-denatured soymilk or soybean powder) and a cosmetic or pharmaceutically acceptable vehicle and, optionally, additional anti-cancer or cosmetically active agents. As used herein, "topically applying" means directly 330 laying on or spreading on outer skin, e.g., by use of the hands or an applicator such as a wipe, roller, or spray.

The phrase "cosmetic or pharmaceutically acceptable" refers to entities and compositions that are  
335 physiologically tolerable and do not typically produce  
an allergic or similar untoward reaction when  
administered to a human. As used herein, "cosmetically  
acceptable" means that the ingredients which the term  
describes are suitable for use in contact with tissues  
340 (e.g., the skin) without undue toxicity,  
incompatibility, instability, irritation, allergic  
response, and the like.

The term "vehicle" refers to a diluent, adjuvant,  
excipient, or carrier. Such cosmetic or pharmaceutical  
345 vehicles can be liquids, such as water and oils,  
including those of petroleum, animal, vegetable or  
synthetic origin, such as peanut oil, soybean oil,  
mineral oil, sesame oil and the like. In the art of  
formulating skin care compositions, the vehicle is often  
350 an oil-in-water or a water-in-oil emulsion. Suitable  
pharmaceutical carriers are described in "Remington's  
Pharmaceutical Sciences" by E.W. Martin. Suitable  
cosmetic carriers are described below.

The compositions for use in the methods of the  
355 present invention include formulations suitable for  
topical application to skin. In one embodiment, the  
composition comprises a non-denatured soy product and a  
cosmetically acceptable topical carrier. In one  
embodiment, the cosmetically acceptable topical carrier  
360 is from about 50% to about 99.99%, by weight, of the  
composition (e.g., from about 80% to about 99%, by  
weight, of the composition).

The compositions may be made into a wide variety of  
product types that include, but are not limited to,  
365 solutions, lotions, creams, gels, sticks, sprays,  
ointments, cleansing liquid washes, solid bars,

shampoos, pastes, foams, powders, mousses, shaving  
creams, wipes, patches, nail lacquers, wound dressing,  
adhesive bandages, hydrogels, and films. Make-up, such  
370 as foundations, mascaras, and lipsticks also form  
suitable compositions. These product types may comprise  
several types of cosmetically acceptable topical  
carriers including, but not limited to solutions,  
emulsions (e.g., microemulsions and nanoemulsions),  
375 gels, solids and liposomes. Certain non-limitative  
examples of such carriers are set forth hereinbelow.  
Other suitable carriers may be formulated by those of  
ordinary skill in the art.

Topical compositions useful in the subject  
380 invention may be formulated as a solution comprising an  
emollient. Such compositions preferably contain from  
about 1% to about 50% of an emollient(s). As used  
herein, the term "emollient" refers to materials used  
for the prevention or relief of dryness, as well as for  
385 the protection of the skin. A wide variety of suitable  
emollients is known and may be used in the present  
invention. Sagarin, *Cosmetics, Science and Technology*,  
2nd Edition, Vol. 1, pp. 32-43 (1972) and the  
International Cosmetic Ingredient Dictionary and  
390 Handbook, eds. Wenninger and McEwen, pp. 1656-61, 1626,  
and 1654-55 (*The Cosmetic, Toiletry, and Fragrance*  
Assoc., Washington, D.C., 7<sup>th</sup> Edition, 1997) (hereinafter  
"ICI Handbook") contains numerous examples of suitable  
materials.

395 A lotion can be made from such a solution. Lotions  
typically comprise from about 1% to about 20% (e.g.,  
from about 5% to about 10%) of an emollient(s) and from  
about 50% to about 90% (e.g., from about 60% to about  
80%) of water.

400 Another type of product that may be formulated from  
a solution is a cream. A cream typically comprises from  
about 5% to about 50% (e.g., from about 10% to about  
20%) of an emollient(s) and from about 45% to about 85%  
(e.g., from about 50% to about 75%) of water.

405 Yet another type of product that may be formulated  
from a solution is an ointment. An ointment may  
comprise a simple base of animal or vegetable oils or  
semi-solid hydrocarbons. An ointment may comprise from  
about 2% to about 10% of an emollient(s) plus from about  
410 0.1% to about 2% of a thickening agent(s). A more  
complete disclosure of thickening agents or viscosity  
increasing agents useful herein can be found in Sagarin,  
Cosmetics, Science and Technology, 2nd Edition, Vol. 1,  
pp. 72-73 (1972) and the ICI Handbook pp. 1693-1697.

415 The topical compositions useful in the present  
invention may be formulated as emulsions. If the carrier  
is an emulsion, from about 1% to about 10% (e.g., from  
about 2% to about 5%) of the carrier comprises an  
emulsifier(s). Emulsifiers may be nonionic, anionic or  
420 cationic. Suitable emulsifiers are disclosed in, for  
example, in McCutcheon's Detergents and Emulsifiers,  
North American Edition, pp. 317-324 (1986), and the ICI  
Handbook, pp. 1673-1686.

Lotions and creams can be formulated as emulsions.  
425 Typically such lotions comprise from 0.5% to about 5% of  
an emulsifier(s). Such creams would typically comprise  
from about 1% to about 20% (e.g., from about 5% to about  
10%) of an emollient(s); from about 20% to about 80%  
(e.g., from 30% to about 70%) of water; and from about  
430 1% to about 10% (e.g., from about 2% to about 5%) of an  
emulsifier(s).

Single emulsion skin care preparations, such as  
lotions and creams, of the oil-in-water type and water-

in-oil type are well known in the cosmetic art and are  
435 useful in the present invention. Multiphase emulsion  
compositions, for example the water-in-oil-in-water  
type, as disclosed in U.S. Patent No. 4,254,105 and  
4,960,764, may also be useful in the present invention.  
In general, such single or multiphase emulsions contain  
440 water, emollients, and emulsifiers as essential  
ingredients.

The topical compositions of this invention can also  
be formulated as a gel (e.g., an aqueous, alcohol,  
alcohol/water, or oil gel using a suitable gelling  
445 agent(s)). Suitable gelling agents for aqueous gels  
include, but are not limited to, natural gums, acrylic  
acid and acrylate polymers and copolymers, and cellulose  
derivatives (e.g., hydroxymethyl cellulose and  
hydroxypropyl cellulose). Suitable gelling agents for  
450 oils (such as mineral oil) include, but are not limited  
to, hydrogenated butylene/ethylene/styrene copolymer and  
hydrogenated ethylene/propylene/styrene copolymer. Such  
gels typically comprise between about 0.1% and 5%, by  
weight, of such gelling agents.

455 The topical compositions of the present invention  
can also be formulated as a solid formulation (e.g., a  
wax-based stick, soap bar composition, powder, or a wipe  
containing powder).

Liposomal formulations are also useful compositions  
460 of the subject invention. In one embodiment, the soymilk  
or soybean powder particles or soy proteins such as STI  
are contained within the liposome. Examples of  
liposomes are unilamellar, multilamellar, and  
paucilamellar liposomes, which may or may not contain  
465 phospholipids. Such compositions can be prepared by  
first combining the non-denatured soy milk product or  
the STI with a phospholipid, such as

dipalmitoylphosphatidyl choline, cholesterol and water. An example of a method for producing liposomes is described in Mezei & Gulasekharam, "Liposomes--A Selective Drug Delivery System for the Topical Route of Administration; Gel Dosage Form", Journal of Pharmaceutics and Pharmacology, Vol. 34 (1982), pp. 473-474. Those of skill in the art may make suitable modifications of the method described therein.

Epidermal lipids of suitable composition for forming liposomes may be substituted for the phospholipid. The liposome preparation may then be incorporated into one of the above carriers (e.g., a gel or an oil-in-water emulsion) in order to produce the liposomal formulation. Other compositions and uses of topically applied liposomes are described in Mezei, M., "Liposomes as a Skin Drug Delivery System", Topics in Pharmaceutical Sciences (D. Breimer and P. Speiser, eds.), Elsevier Science Publishers B. V., New York, N.Y., 1985, pp. 345-358, PCT Patent Application No. WO96/31194, Niemiec, et al., 12 Pharm. Res. 1184-88 (1995), and U.S. Patent No. 5,260,065.

In one embodiment, the liposome is nonionic. In one example, the liposome contains (a) glycerol dilaurate; (b) compounds having the steroid backbone found in cholesterol; and (c) fatty acid ethers having from about 12 to about 18 carbon atoms. In a further embodiment, the liposome comprises glycerol dilaurate, cholesterol, polyoxyethylene-10-stearyl ether, and polyoxyethylene-9-lauryl ether. In one embodiment, these ingredients are in a ratio of about 38:12:33:17.

In one embodiment, the liposomes are present in the topical composition in an amount, based upon the total volume of the composition, of from about 5 mg/ml to

about 100 mg/ml such as from about 10 mg/ml to about 50 mg/ml.

The topical compositions useful in the subject invention may contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials conventionally used in compositions for use on skin, hair, and nails at their art-established levels.

In addition to such agents, other emollients and surface active agents can be incorporated in the emulsions, including glycerol trioleate, acetylated sucrose distearate, sorbitan trioleate, polyoxyethylene (1) monostearate, glycerol monooleate, sucrose distearate, polyethylene glycol (50) monostearate, octylphenoxypoly (ethyleneoxy) ethanol, decaglycerin penta-isostearate, sorbitan sesquioleate, hydroxylated lanolin, lanolin, triglyceryl diisostearate, polyoxyethylene (2) oleyl ether, calcium stearoyl-2-lactylate, methyl glucoside sesquistearate, sorbitan monopalmitate, methoxy polyethylene glycol-22/dodecyl glycol copolymer (Elfacos E200), polyethylene glycol-45/dodecyl glycol copolymer (Elfacos ST9), polyethylene glycol 400 distearate, and lanolin derived sterol extracts, glycol stearate and glycerol stearate; alcohols, such as cetyl alcohol and lanolin alcohol; myristates, such as isopropyl myristate; cetyl palmitate; cholesterol; stearic acid; propylene glycol; glycerine, sorbitol and the like.

The pharmaceutical or cosmetic composition may be optionally combined with other ingredients such as moisturizers, cosmetic adjuvants, anti-oxidants, depigmenting agents, darkening agents, anti-aging agents, hair removal agents, hair styling agents, nail styling agents, sunscreens, surfactants, bleaching



535 agents, foaming agents, conditioners, humectants,  
fragrances, colorants, viscosifiers, buffering agents,  
preservatives, and the like and mixtures thereof. Skin-  
care compositions including these components should be  
formulated so as not to affect the soy product or soy  
540 trypsin inhibitory activity.

Examples of humectants include glycerol, sorbitol,  
propylene glycol, ethylene glycol, 1,3-butylene glycol,  
polypropylene glycol, xylitol, malitol, lactitol,  
allantoin, acetamine MEA, oat protein, hyaluronic acid,  
545 and the like. They may be used either singly or in  
combination.

Because the compositions of this invention are non-  
denatured, i.e., compositions in which the protease  
inhibitory activity is retained, they may be more  
550 favorable as a medium for microbial growth.  
Preservatives are useful for substantially preventing  
microbial decomposition. Examples of preservatives  
include phenoxyethanol and parabens such as methyl-  
paraben, ethyl-paraben, and propyl-paraben; salicylic  
555 acid, chlorhexidine hydrochloride, phenoxyethanol,  
sodium benzoate, methyl para-hydroxybenzoate, ethyl  
para-hydroxybenzoate, propyl para-hydroxybenzoate, butyl  
para-hydroxybenzoate, isothiazolones and the like. Other  
examples of preservatives are listed on pages 1654-55 of  
560 the International Cosmetic Ingredient Dictionary and  
Handbook, eds. Wenninger and McEwen (CTFA, 7<sup>th</sup> ed., 1997),  
hereinafter referred to as the "Cosmetic Handbook." The  
composition may comprise from about 0.01% to about 20%,  
by weight (more preferably, from about 0.5% to about 5%,  
565 by weight) of preservative. Microbial contamination can  
also be eliminated by gamma irradiation or  
microfiltration, or by brief heat treatments that do not

result in the elimination of protease inhibitory activity.

570           Examples of fragrances and odor masks include menthol, anethole, carvone, eugenol, limonene, ocimene, n-decylalcohol, citronellol,  $\alpha$ -terpineol, methyl salicylate, methyl acetate, citronellyl acetate, cineole, linalool, ethyl linalool, vanillin, thymol, 575           spearmint oil, peppermint oil, lemon oil, orange oil, sage oil, rosemary oil, cinnamon oil, pimento oil, cinnamon leaf oil, perilla oil, wintergreen oil, clove oil, eucalyptus oil and the like.

          Examples of surface active agents include sodium 580           alkyl sulfates, e.g., sodium lauryl sulfate and sodium myristyl sulfate, sodium N-acyl sarcosinates, e.g., sodium N-lauroyl sarcosinate and sodium N-myristoyl sarcosinate, sodium dodecylbenzenesulfonate, sodium hydrogenated coconut fatty acid monoglyceride sulfate, 585           sodium lauryl sulfoacetate and N-acyl glutamates, e.g., N-palmitoyl glutamate, N-methylacyltaurin sodium salt, N-methylacylalanine sodium salt, sodium  $\alpha$ -olefin sulfonate and sodium dioctylsulfosuccinate; N-alkylaminoglycerols, e.g., 590           N-lauryldiaminoethylglycerol and N-myristyldiaminoethylglycerol, N-alkyl-N-carboxymethylammonium betaine and sodium 2-alkyl-1-hydroxyethylimidazoline betaine; polyoxyethylenealkyl ether, polyoxyethylenealkylaryl 595           ether, polyoxyethylenelanolin alcohol, polyoxyethyleneglyceryl monoaliphatic acid ester, polyoxyethylenesorbitol aliphatic acid ester, polyoxyethylene aliphatic acid ester, higher aliphatic acid glycerol ester, sorbitan aliphatic acid ester, 600           Pluronic™ type surface active agent, and polyoxyethylenesorbitan aliphatic acid esters such as

polyoxyethylenesorbitan monooleate and  
polyoxyethylenesorbitan monolaurate.

605 Examples of the binder or thickener include  
cellulose derivatives such as alkali metal salts of  
carboxymethylcellulose, methyl cellulose, hydroxyethyl  
cellulose and sodium carboxymethylhydroxyethyl  
cellulose, alkali metal alginates such as sodium  
alginate, propylene glycol alginate, gums such as  
610 carrageenan, xanthan gum, tragacanth gum, caraya gum and  
gum arabic, and synthetic binders such as polyvinyl  
alcohol, polysodium acrylate and polyvinyl pyrrolidone.  
Thickening agents that can be added to the compositions  
of this invention to alter viscosity include other  
615 polymers such as polyacrylates (e.g., polyacrylamide).  
Other examples of viscosity modifying agents are listed  
on pages 1692-97 of the Cosmetic Handbook. To achieve  
the appropriate viscosity, compositions of the present  
invention may comprise from about 0.01% to about 20%, by  
620 weight (e.g., from about 0.1% to about 5%, by weight) of  
a thickening agent.

Coloring agents and fragrances also are commonly  
included in such compositions.

625 In one embodiment, the topical composition further  
comprises another cosmetically active agent in addition  
to the non-denatured soy product. A "cosmetically  
active agent" is a compound (e.g., a synthetic compound  
or a compound isolated from a natural source or a  
natural extract) that has a cosmetic or therapeutic  
630 effect on the skin, hair, or nails, including, but not  
limiting to, lightening agents, darkening agents such as  
self-tanning agents, anti-acne agents, shine control  
agents, anti-microbial agents, anti-inflammatory agents,  
anti-mycotic agents, anti-parasite agents, external  
635 analgesics, sunscreens, photoprotectors, antioxidants,

keratolytic agents, detergents/surfactants,  
moisturizers, nutrients, vitamins, energy enhancers,  
anti-perspiration agents, astringents, deodorants, hair  
removers, firming agents, anti-callous agents, and  
640 agents for hair, nail, and/or skin conditioning.

The compositions of this invention may be applied  
prior to, concurrently with or after other active  
ingredients or compositions to enhance their effect.

Antioxidants and/or chelating agents may also be  
645 used to increase shelf life and stability of the  
compositions. Antioxidants may be added both for  
formulation stabilization and for biological efficacy.  
Antioxidant compounds and their derivatives include, but  
are not limited to, water-soluble antioxidants such as  
650 sulfhydryl compounds and their derivatives (e.g., sodium  
metabisulfite and N-acetyl-cysteine), lipoic acid and  
dihydrolipoic acid, resveratrol, acetyl-cysteine  
(Iniferine®) or lactoferrin, and ascorbic acid and  
ascorbic acid derivatives (e.g., ascorbyl palmitate and  
655 ascorbyl polypeptide). Oil-soluble antioxidants  
suitable for use in the compositions of this invention  
include, but are not limited to, butylated  
hydroxytoluene, retinoids (e.g., retinol and retinyl  
palmitate), tocopherols (e.g., tocopherol acetate),  
660 tocotrienols, and ubiquinone. Natural extracts  
containing antioxidants suitable for use in the  
compositions of this invention, include, but not limited  
to, extracts containing flavonoids and isoflavonoids and  
their derivatives (e.g., genistein and diadzein),  
665 extracts containing resveratrol and the like. Examples  
of such natural extracts include grape seed, green tea,  
pine bark, propolis, and legume extracts. Other  
examples of antioxidants may be found on pages 1612-13  
of the Cosmetic Handbook. The compositions of the

670 present invention may comprises the antioxidant in an  
amount of from about 0.001% to about 20%, by weight  
(e.g., from about 0.01% to about 10% by weight) of the  
composition.

It is preferable to have at least one oil-soluble  
675 antioxidant in the compositions of this invention. The  
antioxidants should be utilized in a stabilizing  
effective amount and may range in total from about 0.001  
to 10% based on the weight of the total composition,  
preferably from about 0.005 to about 5%. The  
680 oil-soluble antioxidants which are useful in the  
compositions of the present invention include butylated  
hydroxytoluene (BHT), ascorbyl palmitate, butylated  
hydroxanisole (BHA), phenyl- $\beta$ -naphthylamine,  
hydroquinone, propyl gallate, nordihydroguaiaretic acid,  
685 and mixtures thereof as well as any other known  
oil-soluble antioxidant compatible with the other  
components of the compositions.

Preferably, a water-soluble antioxidant should also  
be present in the water phase of the compositions of  
690 this invention. The water-soluble antioxidants which are  
useful in the compositions of this invention include  
ascorbic acid, sodium metabisulfite, sodium bisulfite,  
sodium thiosulfite, sodium formaldehyde sulfoxylate,  
isoascorbic acid, thioglycerol, thiosorbitol, thiourea,  
695 thioglycolic acid, cysteine hydrochloride,  
1,4-diazobicyclo-(2,2,2)-octane and mixtures thereof as  
well as any other known water-soluble antioxidant  
compatible with the other components of the  
compositions.

700 Chelating agents are also useful in assisting the  
stabilization of the compositions of this invention.  
Examples of chelating agents include EDTA and  
derivatives thereof (e.g., disodium EDTA and dipotassium

EDTA), Iniferine<sup>®</sup>, lactoferrin, and citric acid. Other  
705 examples of chelating agents are listed on page 1626 of  
the Cosmetic Handbook. The compositions of the present  
invention may comprise the chelating agent in an amount  
of from about 0.001% to about 20%, by weight (e.g., from  
about 0.01% to about 10% by weight) of the composition.

710 Other active ingredients such as sunscreen  
materials may be utilized in the compositions of the  
present invention provided that they are physically and  
chemically compatible with the other components of the  
compositions. Sunscreens may include organic or  
715 inorganic sunscreens, such as methoxyoctylcinnamate and  
other cinnamate compounds, titanium dioxide and zinc  
oxide and the like.

Various irritancy mitigants may be added to the  
compositions of this invention. Irritancy mitigants  
720 such as  $\alpha$ -bisabolol, panthenol, allantoin, ginkgo  
biloba, stearyl glycerethetic acid (licorice extract),  
tea tree oil, butchers' broom, calendula, ginseng and  
the like may be added.

Other ingredients may include agents that assist in  
725 protecting the skin from aging, such as sunscreens,  
anti-oxidant vitamins such as ascorbic acid, vitamin B,  
biotin, pantothenic acid, vitamin D, vitamin E and  
vitamin C, and sodium bisulfite. Yeast extract, ginkgo  
biloba, bisabolol, panthenol, alpha hydroxy acids and  
730 oligosaccharides such as melibiose are among other  
ingredients which assist in preventing aging of the skin  
by such means as irritation mitigation, oxidation  
mitigation, healing, affecting retinoid metabolism and  
inhibiting the production of elastase.

735 The compositions of this invention may also contain  
other depigmenting agents in addition to the soy  
product. What is meant by depigmentation is the

lightening of the color of an area of skin, including but not limited to, the global lightening of the user's skin tone/complexion (e.g., the face, hands, or whole body, which is uneven as a result of aging skin, or darker than desired because of ethnicity or pathology, and the like), the evening of skin color tone, or the specific lightening of age spots, freckles, or darker pigmented areas such as, but not limited to, post-inflammatory hyper-pigmentary lesions.

Examples of such depigmenting agents include, but are not limited to, lipoic acid, dihydrolipoic acid, resveratrol, ascorbic acid, kojic acid, hydroquinone, isoflavones, retinoids (e.g., retinol, retinoic acid, and retinyl palmitate), tyrosinase inhibitors, melanosome transfer inhibitors, and selective cytotoxic agents for melanocytes, or natural extracts, e.g., licorice extract, gatuline A (pilewort extract), and micromerol (butylene glycol and apple extract), providing these activities. The amount of the depigmenting agent used will depend on the activity of the compound, and will typically range from about 0.001% to about 20%, by weight (e.g., from about 0.01% to about 10%, by weight) of the composition.

Other skin color evening ingredients, such as skin darkening or sunless tanning agents, may also be effective in the skin care compositions for use in this invention.

The composition of the present invention may also contain compounds that enhance the feel of the composition on the skin of the user. Examples of such compounds include, but are not limited to, oils, silicones (e.g., siloxane polymers such as dimethicone) and skin-conditioning agents such as emollients, and humectants. Examples of such skin conditioning agents

may be found of pages 1656-1670 of the Cosmetic Handbook.

775 Compositions which assist in the reduction of lines and wrinkles may also be added to the compositions of this invention. For example, alpha hydroxy acids, hyaluronic acid, Gatuline R (fagus silvitica extract), pigments and scattering aids such as zinc oxide and titanium dioxide may be used in the compositions of this  
780 invention in this capacity.

Anti-inflammatory agents may also be used in the compositions of this invention. Not only should these agents assist in mitigating irritation, they may assist in treating wrinkles and lines in the skin. Steroidal  
785 anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone- phosphate, beclomethasone dipropionate, clobetasol valerate, desonide, desoxycorticosterone  
790 acetate, dexamethasone, dichlorisone, deflorasonediacetate, diflucortolone valerate, fluadronolone, fluclarolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocionide, flucortine butylester, fluocortolone,  
795 flupredidene (flupredylidene) acetate, flurandronolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide,  
800 medrysone, amciafel, amcinafide, betamethasone and its esters, chlorprednisone acetate, clocortelone, clescinalone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone  
805 cyclopentylpropionate, hydrocortamate, meprednisone,



paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone and mixtures thereof may be used. Preferably, hydrocortisone or natural extracts with similar activity may be used.

810 Nonsteroidal anti-inflammatory agents may also be employed in the compositions of this invention, such as salicylates, acetic acid derivatives, fenamates, propionic acid derivatives and pyrazoles or mixtures thereof. Other synthetic and natural anti-inflammatory  
815 agents may also be used.

Additional active ingredients having topical activity may be utilized in the compositions of this invention. Azole-type anti-fungal and anti-bacterial agents may be employed in the compositions of this  
820 invention in their base form. For example, ketoconazole, miconazole, itraconazole, elubiol, and like related imidazole antifungals and antibacterials are useful in the topical formulations of this invention.

It can be readily appreciated that a transdermal route of administration may be enhanced by use of a  
825 dermal penetration enhancer, e.g., such as enhancers described in U.S. Patent No. 5,164,189, U.S. Patent No. 5,008,110, and U.S. Patent No. 4,879,119, issued November 7, 1989 to Aruga et al. In one embodiment, a  
830 composition of the present invention can be delivered in a controlled release system, such as using a transdermal patch, liposomes, or other modes of administration. In another embodiment, polymeric materials can be used [see Medical Applications of Controlled Release, Langer and  
835 Wise (eds.), CRC Press: Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley: New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al.,

840 Science 228:190 (1985); During et al., Ann. Neurol.  
25:351 (1989); Howard et al., J. Neurosurg. 71:105  
(1989)].

In another embodiment, a controlled release system  
can be placed in proximity of the target tissues of the  
845 mammal, thus requiring only a fraction of the systemic  
dose [see, e.g., Goodson, in Medical Applications of  
Controlled Release, supra, vol. 2, pp. 115-138 (1984)].  
In particular, a controlled release system can be  
introduced into an animal in proximity of the site of  
850 inappropriate immune activation or a tumor. Other  
controlled release systems are discussed in a review by  
Langer [Science 249:1527-1533 (1990)].

In yet another embodiment of the invention, the  
soybean trypsin inhibitor may be produced by recombinant  
855 means. The nucleotide and protein sequences of STI are  
known. See GenBank Accession No. AF314823. Methods for  
recombinant expression of STI are well known to those of  
ordinary skill in the art. In an alternative  
embodiment, the STI so produced may be modified at the  
860 genetic level (e.g. replacing amino acids to change  
local charges, to enhance skin penetration without  
compromising activity, or to enhance activity without  
compromising skin penetration) or chemically post  
synthesis (e.g. additional lipid or sugar groups) to  
865 enhance uptake of the STI into the skin of the patient.

Various and numerous methods are known in the art  
for transdermal administration of a drug, e.g., via a  
transdermal patch. Transdermal patches are described in  
for example, U.S. Patent No. 5,407,713, issued April 18,  
870 1995 to Rolando et al.; U.S. Patent No. 5,352,456,  
issued October 4, 1994 to Fallon et al.; U.S. Patent No.  
5,332,213 issued August 9, 1994 to D'Angelo et al.; U.S.  
Patent No. 5,336,168, issued August 9, 1994 to Sibal;

875 U.S. Patent No. 5,290,561, issued March 1, 1994 to  
Farhadieh et al.; U.S. Patent No. 5,254,346, issued  
October 19, 1993 to Tucker et al.; U.S. Patent No.  
5,164,189, issued November 17, 1992 to Berger et al.;  
U.S. Patent No. 5,163,899, issued November 17, 1992 to  
880 Sibalis; U.S. Patent Nos. 5,088,977 and 5,087,240, both  
issued February 18, 1992 to Sibalis; U.S. Patent No.  
5,008,110, issued April 16, 1991 to Benecke et al.; and  
U.S. Patent No. 4,921,475, issued May 1, 1990 to  
Sibalis.

885 Compositions of the present invention may be  
prepared by mixing the desired ingredients. For example,  
soymilk is mixed with the chelating agent, preservative,  
and/or antioxidant. A thickener is then added to the  
system, and the mixture is further mixed until it reaches  
homogeneity at the desired viscosity. The compositions  
890 of the present invention may be prepared under an argon,  
nitrogen, or other inert gaseous blanket in order to  
enhance formulation stability and/or to reduce soybean  
odor. The compositions of this invention may be packaged  
in a tube, a sealed packet, a jar, a pump, a bottle, a  
895 can, a pledget, a towelet, a wipe or the like. An  
airtight package such as an aluminum tube, aluminum  
pocket, pump, laminate tube, or the like, can also be  
used to further enhance product stability.

900 The skin-care compositions for use in the methods  
of this invention may be applied daily for at least four  
weeks, and more preferably at least eight weeks, and  
most preferably on a continuous regular daily basis.  
Application may be continued as long as desired to  
maintain the condition of the skin and to reduce skin  
905 cancer risk in skin cells that have not yet been  
damaged.

The topically active pharmaceutical or cosmetic

composition should be applied in an amount effective to effect the desired changes in the skin. As used herein, "amount effective" shall mean an amount sufficient to cover the region of skin surface where preventing cancer, inhibiting the growth rate of a cutaneous tumor, or reducing the risk of cancer is desired. Preferably, the composition is applied to the skin surface such that, based upon a  $\text{cm}^2$  of skin surface, from about 2  $\mu\text{l}/\text{cm}^2$  to about 500  $\mu\text{l}/\text{cm}^2$  of topically active agent is present when preventing cancer, inhibiting the growth rate of a cutaneous tumor, or reducing the risk of cancer is desired.

The following examples are provided to describe the invention in further detail. These examples are provided for illustrative purposes only, and are not to be construed as limiting the invention.

#### EXAMPLE 1

##### Preparation of Soymilk from Soybean Powder

160 g of soybean powder (Sunlight Foods, Taipei, Taiwan) was added to about 1440 g of deionized water. The mixture was stirred at room temperature for about 1 hour. The mixture was then filtered through a sieve having holes of  $75\mu\text{m}$  diameter. The filtrate resulted in about 1.1 kg of soymilk.

#### EXAMPLE 2

##### Preparation of Soymilk Gel from Soymilk

The following compositions of this invention were prepared as follows. The weight percentages of each ingredient in the compositions are indicated below in Table 2 and Table 3. First, the soymilk, as prepared in example 3, was placed into a first beaker. The

945 preservative Phenonip® (a mixture of the preservatives methyl-paraben, propyl-paraben, ethyl-paraben, and phenoxy-ethanol sold by NIPA, Wilmington, Delaware) or the preservative phenoxyethanol were added to the soymilk. Next, the chelating agent Disodium EDTA and in some examples the humectant glycerin were added to the first beaker and mixed with the soymilk. It is also possible to further add cyclomethicone, or dimethicone  
950 (tradename Dow Corning 200 Fluid ®), or PolySorbate 20, or Aluminum Starch Octyl Succinate, or Sucrose Cocoate, or PEG-6 Capric/Caprylic Triglycerides to the soymilk mixture at this step as required in some examples in Table 2 and Table 3. A mixture of the thickener  
955 polyacrylamide, laureth-7, and C13-14 isoparaffins (sold by Seppic, Paris, France under the Tradename Sepigel®) was added to a second beaker along with the anti-oxidant BHT. The ingredients in the second beaker were then added to the ingredients of the first beaker and mixed  
960 until homogenous. The anti-oxidants ascorbic acid, sodium ascorbyl phosphate, lactoferrin, or tocopherol were then added to the beaker and homogeneously mixed to form the resulting gel.

965

### EXAMPLE 3

#### Preparation of Soymilk Gel from Soybean Powder, Soymilk Powder or Soybean Extract

The following compositions of this invention were prepared as follows. The weight percentage of each  
970 ingredient in each of the preparations is indicated below in Table 3. First, the soymilk powder (Devansoy Farms, Carroll, IA) or the soybean powder (Sunlight Foods, Taipei, Taiwan) or the Soybean Extract and deionized water were placed into a first beaker and  
975 mixed to reconstitute the soy powder. The preservative

Phenonip® and the chelating agent Disodium EDTA were then added to the first beaker and mixed with the soymilk. A mixture of polyacrylamide, laureth-7, and C13-14 isoparaffins was added to a second beaker along with the anti-oxidant BHT. The ingredients in the second beaker were then added to the ingredients of the first beaker and mixed until homogenous.

#### Example 4

##### **Non-denatured soymilk reduces the formation of UV-induced DNA and cellular damage**

Non-denatured soymilk ("soymilk") was prepared as a 10% suspension in deionized water. 100 grams of soybeans (Oriental Mascot Soybeans imported from China, NY, NY) were hydrated overnight in one liter of water. Soybeans were rinsed in water and then processed in one liter of water using a standard juice extractor. The fine suspension ("milk") was collected and filtered through cheesecloth. The preservative phenoxyethanol (Phenonip, NIPA Hardwicke Inc., Wilmington, DE) was added as 1% of the total volume and the soymilk was stored at 4°C.

Dark skinned Yucatan microswine (Charles River, Maine) were housed in appropriately sized cages in an environmentally controlled room with a 12-hour light - 12-hour dark cycle and supplied with Purina mini-swine chow and water *ad libitum*. Animal care was based on the "Guide for the Care and Use of Laboratory Animals", NIH Publication No. 85-23. Treatments of individual swine were always arranged in a head to tail order on one side, and in a tail to head order on the other side of the animal. A Minimal Erythemic Dose (MED) of UVB was determined for each swine by placing a plastic template

1010 with 1x1 inch<sup>2</sup> cutouts on the dorsum of the swine. Using  
a UVB lamp (Model UVM-57, 302nm lamp, UVP Inc., Upland,  
CA) placed on the template, sites were exposed to UVB  
for increasing times, every other day for five days.  
Unexposed sites were covered with the same material as  
1015 the template. One MED was established as the dose that  
produces the least amount of visible erythema. For DNA  
damage studies, swine were exposed to 1.5 MED, once.  
Soymilk (20□L) was applied twice a day, to a 2.5 cm<sup>2</sup>  
area, for five days prior to UVB exposure, and biopsies  
1020 were taken 24 hr post UVB treatment using standard  
techniques. To prevent a possible sunscreen effect the  
treated sites were cleaned with water to remove all  
visible residual soymilk and allowed to dry prior to the  
UVB exposure.

1025 Skin biopsies were processed for histology and stained  
with Hematoxylin and Eosin (H&E), using standard  
procedures (Sheenan and Hrapckak, 1980). T-T dimer  
staining of swine skin sections was performed by Paragon  
BioServices, Inc. (Baltimore, MD) using primary  
1030 antibodies from Affitech (Oslo Research Park, Oslo,  
Norway). Apoptosis staining (TUNEL) was performed by  
Paragon Bioservices using Terminal Transferase, and  
Biotin-16-dUTP from Roche Diagnostics GmbH, (Mannheim,  
Germany).

1035 Twenty-four hours after one UVB (1.5 MED) exposure  
of swine skin, T-T dimers were documented histologically  
in the epidermis. Pretreatment with soymilk for 5 days,  
once a day (20□l/2.5 cm<sup>2</sup>), reduced, or completely  
eliminated the histologically detectable T-T dimers in  
1040 the swine's epidermis. Similarly, apoptotic cells were  
documented in the epidermis following the same UVB  
treatment, but their presence was reduced or eliminated  
when the skins were pretreated with soymilk prior to UVB

irradiation.

1045           This example demonstrates that pretreatment with  
non-denatured soy extracts prevents or reduces the UV-  
induced cellular and DNA damage, that are known to be  
involved in the formation of skin cancer. Therefore,  
such a pretreatment would reduce or prevent the risk of  
1050 UV-induced skin cancer.

          While certain preferred embodiments of the present  
invention have been described and specifically  
exemplified above, it is not intended that the invention  
be limited to such embodiments. Various modifications  
1055 may be made thereto without departing from the scope and  
spirit of the present invention, as set forth in the  
following claims.